HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation.

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Public Summary:
We find that treatment of a mouse model of Huntington's disease (HD) with HDAC inhibitors has beneficial effects on the offspring of treated animals. We also map epigenetic differences in human tissues from HD patients, suggesting that HDAC inhibitors may be of use in treating HD.

Scientific Abstract:
Increasing evidence has demonstrated that epigenetic factors can profoundly influence gene expression and, in turn, influence resistance or susceptibility to disease. Epigenetic drugs, such as histone deacetylase (HDAC) inhibitors, are finding their way into clinical practice, although their exact mechanisms of action are unclear. To identify mechanisms associated with HDAC inhibition, we performed microarray analysis on brain and muscle samples treated with the HDAC1/3-targeting inhibitor, HDACi 4b. Pathways analyses of microarray datasets implicate DNA methylation as significantly associated with HDAC inhibition. Further assessment of DNA methylation changes elicited by HDACi 4b in human fibroblasts from normal controls and patients with Huntington's disease (HD) using the Infinium HumanMethylation450 BeadChip revealed a limited, but overlapping, subset of methylated CpG sites that were altered by HDAC inhibition in both normal and HD cells. Among the altered loci of Y chromosome-linked genes, KDM5D, which encodes Lys (K)-specific demethylase 5D, showed increased methylation at several CpG sites in both normal and HD cells, as well as in DNA isolated from sperm from drug-treated male mice. Further, we demonstrate that first filial generation (F1) offspring from drug-treated male HD transgenic mice show significantly improved HD disease phenotypes compared with F1 offspring from vehicle-treated male HD transgenic mice, in association with increased Kdm5d expression, and decreased histone H3 Lys4 (K4) (H3K4) methylation in the CNS of male offspring. Additionally, we show that overexpression of Kdm5d in mutant HD striatal cells significantly improves metabolic deficits. These findings indicate that HDAC inhibitors can elicit transgenerational effects, via cross-talk between different epigenetic mechanisms, to have an impact on disease phenotypes in a beneficial manner.